REMARKS

Enclosed herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a second Substitute Sequence Listing to be inserted into the specification as indicated above. The second Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a disk copy of the Substitute Sequence Listing. The disk copy of the Sequence Listing, file "2001-11-13 3631-0109P CRF.txt", is identical to the paper copy, except that it lacks formatting.

Sequences disclosed in the application that were not previously made part of the Sequence Listing as originally filed on April 4, 2001 have been included in the second Substitute Sequence Listing enclosed herewith. The newly added sequences are found in Figures 5b and 6 which are submitted concurrently herewith and part of the original International Application PCT/DK99/00525 of which the present application is a National Stage Application pursuant to 35 U.S.C 371. The amendments are being made to reference the sequences by their SEQ ID NOs. No new matter is introduced by these amendments.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Leonard R. Svensson, #30,330

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

LRS/SWG/CAV
3631-0109P

Attachments:
Version with Markings to Show Changes Made
Disk Copy of Sequence Listing
Paper Copy of Sequence Listing
Copy of Notification of Defective Response

VERSION WITH MARKINGS TO SHOW CHANGES MADE

(**added material** is noted in bold underline; [deleted material] is noted in brackets)

In the Specification:

Please replace the paragraph beginning on page 14, line 12, with the following rewritten paragraph:

--Fig. 5: The FGF genes and proteins. A: Exon-intron structure of the human and mouse FGF8 genes. Below is illustrated the eight different splice forms (from Gemel 1996). B: Amino acid sequence **(SEQ ID NO: 34)** of the different FGF8 isoforms. The polypeptide stretches unique to FGF8b, FGF8f, and FGF8e are indicated by bold and italic or underlined typefaces. FGF8a is the shortest variant containing none of these highlighted sequences. The signal peptide is expected to be cleaved C-terminally to Ala22. The two cysteine residues found in mature FGF8(all isoforms) are indicated by thick underlining. The two potential N-glycosylation sites of FGF8b are indicated by Ñ. Numbering is according to FGF8b.--

Please replace the paragraph beginning on page 14, line 25, with the following rewritten paragraph:

--Fig. 6: Illustrations of the four different variants of FGF8b designed for autovaccination. Upper panel: Theoretical models of the insertion-points of the epitopes using the FGF2 crystal structure as template. Lower panel: Amino acid sequences of the wild type FGF8b (WT) and the four variants F30N, F2I, F33I, and F2C **(SEQ ID NOS: 35-39, respectively)**. The signal peptide is marked with single underlining. The inserted peptides are marked with double underlining. The N-terminal sequence (MetAla) of all variants is due to generation of a Kozak-sequence (Kozak 1991) for better translation in eukaryotic systems.--

Please replace the paragraph beginning on page 31, line 17, with the following rewritten paragraph:

--One especially preferred PADRE peptide is the one having the amino acid sequence AKFVAAWTLKAAA **(SEQ ID NO: 40)** or an immunologically effective subsequence thereof. This, and other epitopes having the same lack of MHC restriction are preferred T-cell epitopes which should be present in the analogues used in the inventive method. Such super-promiscuous epitopes will allow for the most simple embodiments of the invention wherein only one single analogue is presented to the vaccinated animal's immune system.--

Please replace the paragraph beginning on page 89, line 22, with the following rewritten paragraph:

--Hence, an important embodiment of the methods of the invention is one wherein the foreign T-cell epitope is introduced in a part of the Her2 amino acid sequence defined

by the amino acid numbering in SEQ ID No: 5 **(also shown in SEQ ID NO: 4)** positions 5-25 and/or 50-73 and/or 103-117 and/or 149-163 and/or 210-224 and/or 250-264 and/or 325-339 and/or 369-385 and/or 465-479 and/or 579-593 and/or 632-652 and/or 653-667 and/or 661-675 and/or 695-709 and/or 710-730, cf. the Examples.--

Please replace the paragraph beginning on page 94, line 7, with the following rewritten paragraph:

--FGF8b has by several investigators been shown very efficient in inducing the transformation of NIH3T3 or SC115 cells (Miyashita 1994, Kouhara 1994, Lorenzi 1995, MacArthur 1995a). By using recombinantly expressed proteins, it has also been shown that this induction of morphological changes is far more efficient with FGF8b than when using FGF8a or FGF8c (MacArthur 1995a, Ghosh 1996). Interestingly, the N-terminal half of the FGF8b molecule alone, was shown to be sufficient for transformation of NIH3T3 cells, and even the small FGF8b specific peptide (QVTVQSSPNFT) **(SEQ ID NO: 41)** could enable the cells to grow 2-3 times longer than normal in 0.1% serum (Rudra-Ganguly 1998). Furthermore, NIH3T3 cells stably transfected with an expression vector encoding FGF8b has been reported to be very tumorigenic when injected intraocularly into nude mice (Kouhara 1994, Ghosh 1996).--

Please replace the paragraph beginning on page 101, line 29, with the following rewritten paragraph:

--Hence, the invention also relates to embodiments of the methods described herein where, where the foreign T-cell

epitope is introduced in a part of the FGFrb amino acid sequence defined by SEQ ID NO: 6 **(encoded by nucleotide sequence SEQ ID NO: 5)** positions 1-54 and/or 178-215 and/or 55-58 and/or 63-68 and/or 72-76 and/or 85-91 and/or 95-102 and/or 106-111 and/or 115-120 and/or 128-134 and/or 138-144 and/or 149-154 and/or 158-162 and/or 173-177. It should be noted that it is especially preferred not to introduce variations or modifications in positions 26-45 and in the C-terminus starting at amino acids 186-215, since these stretches show the least homology with a recently discovered protein, FGF-18, which seems to be expressed in a variety of non-tumour tissues.--

Please replace the paragraph beginning on page 114, line 1, with the following rewritten paragraph:

--The expressed hPSM mutant proteins will be designated PROS__.__, where the first __ is the insertion region used for insertion of P2, and the second __ is the insertion region used for P30. If P2 or P30 is not present in the protein, the number 0 (zero) is designated. The wild type hPSM is designated PROS0.0. PROS110.0 is the hPSM amino acids 437-750 protein product. HIS tagged proteins are called HIS-PROS__.__. As His tags has been used SEQ ID NO: 21 **(amino acid sequence shown in SEQ ID NO:22)** for expression in yeast and bacteria, whereas SEQ ID NO: 23 **(amino acid sequence shown in SEQ ID NO: 24)** has been used for expression in mammalian cells.--

Please replace the paragraph beginning on page 117, line 21, with the following rewritten paragraph:

--A strain of *Pichia pastoris* as well as two different expression vectors have been purchased from Invitrogen. The vector pPICZ∀A carries a methanol inducible promoter upstream of the polycloning site, whereas the pGAPZ∀A vector express proteins constitutively. Both vectors encode the ∀-factor secretion signal in order to export the recombinant proteins to the medium. The selection system of these vectors is zeocin resistance. The sequences encoding hPSM0.0, and hPSM'0.0 (as well as one hPSM mutant, hPSM1.1, cf. below) were subcloned into these vectors (in-frame with a C-terminal c-myc identification epitope, SEQ ID NO: 27 **(amino acid sequence shown in SEQ ID NO: 28)**).--

Please replace the paragraph beginning on page 138, line 16, with the following rewritten paragraph:

--Currently, various DNA vaccination experiments are ongoing using hPSM constructs. Various human PSM wildtype and AutoVac constructs (such as e.g. hPSM0.0, hPSM'0.0, hPSM'0.0, hPSM1.1, hPSM1C.3) have been subcloned into DNA vaccination vectors (such as pcDNA3.1(+), pcDNA3.1(-), pVAX and pZeoSV2). In some of the constructions, different leader sequences (such as the CD11a, tPA, and IL-5 leader sequences; **nucleotide** SEQ ID NOS: 29, 25, and 31, **and amino acid SEQ ID NOS: 30, 26, and 32,** respectively) have been included directly N-terminally and in-frame to allow secretion of the expressed hPSM proteins in vivo. All the constructions in DNA vaccination vectors have been verified by DNA sequencing and in vitro translation.--

Please replace the paragraph beginning on page 153, line 16, with the following rewritten paragraph:

--The internal variants of FGF8b (F30I and F2I) were constructed by replacing external loops in the FGF2 structure with the epitopes [P2 and P30] **P30 and P2**, respectively, whereby the beta-barrel structural backbone of the FGF structure presumably will remain unchanged.--